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Stable gel comprising neutralised chitosan and poly(N-vinyl lactam) - has hydrophilic absorbent property and is useful in wound and burn dressings, drug delivery systems and cosmetic masks and wraps

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• **Abstract :**

US5420197 A A dermatologically-compatible compsn. comprises a hydrophilic gel which comprises a blend of neutralised chitosan and a hydrophilic poly(N-vinyl lactam) having a K value at least 60 and > 1.4 mole equivalents of available acid gps.

Also claimed is a method for preparing a stable, mildly tacky hydrophilic gel.

The poly(N-vinyl lactam) comprises polyvinylpyrrolidone homopolymer, copolymer or terpolymer, pref. has at least 2.0 mole equivalents of available acid gps. and is obtd. by ring opening lactam gps.

Ring opening is effected by heating the poly(N-vinyl lactam) in aq. soln. at 50-200 deg. C and 15-150 psi for one half hour to 10 days.

The gel pref. includes at least one additional ingredient which may be releasable from the gel e.g. a fragrance or a biologically active material selected from nitroglycerine, scopolamine, pilocarpine, ergotamine tartrate, phenylpropanolamino, theophylline, tetracycline, neomycin, oxytetracycline, triclosan, sodium cefazolin, silver sulphodiazine, salicylates, ricotinates, capsaicin and benzocaine.

The gel may be combined with one or more substrates, e.g. a polymer film, collagen film, woven fabric or non-woven fabric.

USE - The gel is useful in wound packings, wound dressings, burn dressings, drug delivery dressings, dry films, cosmetic mask dressings and cosmetic wrap dressings.

ADVANTAGE - The gel is stable and has a hydrophilic absorbent property: unlike hydrocolloid dressings, it is able to absorb exudate without losing its gel structure.

The gel can be produced without a need for expensive equipment and/or processing. (Dwg.0/0)

EP-663212 B A dermatologically-compatible compsn. comprises a hydrophilic gel which comprises a blend of neutralised chitosan and a hydrophilic poly(N-vinyl lactam) having a K value at least 60 and > 1.4 mole equivalents of available acid gps.

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AU9480382 A 19950720 DW1995-37 A61K-009/06 AP: 1994AU-0080382 19941213

CA2138351 A 19950714 DW1995-40 A61L-015/28 AP: 1994CA-2138351 19941216

JP07250886 A 19951003 DW1995-48 A61L-015/64 7p AP: 1995JP-0003794 19950113

EP-663212 A3 19950906 DW1996-14 C08G-063/48 AP: 1995EP-0200068 19950112

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EP-663212 B1 19980415 DW1998-19 A61K-047/36 Eng 9p AP: 1995EP-0200068 19950112 DSR: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

MX-184762 B 19970526 DW1998-23 C08G-063/048 AP: 1995MX-0000475 19950113

DE69502029 E 19980520 DW1998-26 A61K-047/36 FD: Based on EP-663212 AP: 1995DE-6002029 19950112; 1995EP-0200068 19950112

ES2117825 T3 19980816 DW1998-39 A61K-047/36 FD: Based on EP-663212 AP: 1995EP-0200068 19950112

TW-388716 A 20000501 DW2000-62 A61L-015/24 AP: 1995TW-0100231 19950311

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(54) Gels formed by the interaction of polyvinylpyrrolidone with chitosan derivatives

Gel geformed durch die Interaktion von Polyvinylpyrrolidon mit Chitosan-Derivativen

Gels obtenus par l'interaction de la polyvinylpyrrolidone et de dérivés chitosane

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(56) References cited:
EP-A- 0 486 294
EP-A- 0 506 300
US-A- 4 603 048
US-A- 4 780 310

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Description

BACKGROUND OF THE INVENTION

This invention relates to the field of poly(N-vinyl lactam)-chitosan gels and more particularly to gels which are absorbent and may be skin adhering, which are flexible and contour-conforming, and which can be used for a variety of applications.

Chitosan is a deacetylated chitin, and is a linear polysaccharide of deacetylated N-acetyl-D-glucosamine. Chitosan has been used to absorb heavy metals from water and industrial waste streams, and as a dyeing assistant in photographic emulsions. Chitosan derivatives have also been used in cosmetics and conditioning agents, in hair setting lotions and shampoos as, for example, in U.S. Patent Nos. 4,134,412 and 4,202,881, when neutralized with acids.

Poly(N-vinyl lactam)s such as polyvinylpyrrolidone (PVP) have been used, for example, in pharmaceuticals, in certain types of films and in some cosmetic products.

It has been known that polyvinylpyrrolidone forms complexes with polyurethanes to yield hydrophilic blends or alloys. U.S. Patent No. 4,642,267 describes hydrophilic polymer blends of polyurethane and hydrophilic poly(N-vinyl lactam) prepared in solvent solution to provide slippery coatings when wet and which are water insoluble to some extent once cured by drying.

European Patent Application 107,376 describes tacky PVP gels which require the use of ionizing radiation for cross-linking. U.S. Patent No. 4,646,730 describes a PVP/Silver Sulfadiazine hydrogel dressing in which electron beam radiation is required to cross-link the PVP and form a gel. In addition, magnesium trisilicate, hydrogen peroxide and/or polyacrylic acid are added for color stabilization. It is apparent that there would be an advantage in making skin-adhering gels in the absence of expensive equipment and/or processing.

Ring opening of pyrrolidone groups on PVP was described by H.P. Frank, "The Lactam-Amino Acid Equilibria for Ethylpyrrolidone and Polyvinylpyrrolidone", Journal of Polymer Science 12, 565-576 (1954), and A. Conex and G. Smets, "Ring Opening in Lactam Polymers", J. Poly. Chem. 13, 221-229 (1955). The concept of ring-opened pyrrolidone groups is made use of in this invention to unexpectedly attain absorbent gels.

It is therefore an object of the invention to provide dermatologically-compatible gels having a hydrophilic absorbent property.

It is a further object to produce gels without a need for expensive equipment and/or processing.

It is another object to provide gels of poly(N-vinyl lactam) and chitosan derivatives which can be used in a variety of products such as cavity dressings, drug delivery patches, face masks and wound dressings.

SUMMARY OF THE INVENTION

Accordingly, there is provided a stable, hydrophilic gel which comprises a blend of acid-neutralized chitosan and a poly(N-vinyl lactam), with or without a plasticizer, the poly(N-vinyl lactam) having a K value of at least about 60 and mole equivalents of acid groups of at least 2.0. The gel may be formed into a wound packing or cavity dressing where, unlike hydrocolloid dressings, it is able to absorb exudate without losing its gel structure. It can also be utilized as a drug carrier for transdermal devices and for use in dry skin masks to deliver moisturizers to the skin.

The poly(N-vinyl lactam) is preferably a polyvinylpyrrolidone having mole equivalents of acid groups of at least about 1.4 formed by ring opening of pyrrolidone groups.

While ring opening of lactam groups, such as pyrrolidone groups in polyvinylpyrrolidone (PVP), is one possible source of acid groups (specifically carboxyl groups), it is not the only source. For example, ring opening of pyrrolidone groups in vinylpyrrolidone monomers can result from hydrolysis reactions yielding carboxyl containing monomers which will polymerize with vinylpyrrolidone during the manufacture of PVP. Also, certain polymerization catalysts such as perbenzoic acid will result in carboxyl end groups in PVP polymer chains.

The gel is prepared by mixing aqueous poly(N-vinyl lactam) solution and acid-neutralized chitosan in aqueous solution at a poly(N-vinyl lactam)/chitosan weigh of from 12/1 to 2/1, preferably from 10/1 to 5/1, to form a blend at 5 wt.% to 20 wt.% total polymer concentration, preferably from 7.5 wt.% to 15 wt.% polymer concentration, and allowing the blend to cure until a gel is formed.

The gel preferably includes at least one additional ingredient which may be releasable from the gel. Preferably the releasable ingredient is a moisturizer, drug or other bio-effecting or body-treating material.

Preferred products for which the dressing may be used are cavity-filling wound dressings, other wound and burn dressings, drug delivery systems, and cosmetic masks and wraps.

For a better understanding of the present invention, together with other and further objects, reference is made to the following description, and its scope will be pointed out in the appended claims.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

It has been found that poly(N-vinyl lactam) such as polyvinylpyrrolidone (PVP), with a degree of ring-opened pyrrolidone groups, forms hydrophilic gels with chitosans. The gels are flexible and transparent or translucent and may be used alone or with various additives. The gels can be used for wound packing, wound and burn dressings, drug delivery systems, cosmetic

face and nail wraps, and other applications where the high absorption capacity of the gel and the high heat capacity and transport capacity of water as part of the hydrophilic gel can be utilized. These gels may have either a tacky quality or a non-tacky quality.

Chitosan, a natural product, is derived from chitin. Chitin is an unbranched linear polysaccharide of N-acetyl-D-glucosamine units linked by β-1,4 bonds. It is a polymer of glucose in which the hydroxyl group on C-2 is replaced by the N-acetylamino group -$NHCOCH_3$. In chitosan, the acetyl group is absent. Therefore, chitosan is a deacetylated chitin. Chitosan contains approximately 7% nitrogen and is structurally similar to cellulose. Chitin occurs in nature in the exoskeletons of arthropods such as crabs, lobsters and shrimp. Chitin can be obtained from these sources as an amorphous powder after dissolution of the calcium carbonate with mineral acids and removal of the proteins. It is also found in some fungi, algae and yeasts.

Chitosan becomes soluble in water when protonated with acids. The polymer thus formed is positively charged and thus more likely to interact with negatively charged surfaces like skin and hair.

Chitosan derivatives are commercially available as, for example, chitosan neutralized with pyrrolidone carboxylic acid available as Kytamer PCA^R from Amerchol Corporation; carboxymethyl sodium salt of chitosan available as Chitisol^R from Muto Corporation; chitosan neutralized with glutamic acid available as Seacure + 210^R from Protan Corporation; N,O-carboxymethyl chitosan available from Nova Chem. Ltd., Canada; and unneutralized chitosan available from Tokyo Kasei Inc. Suitable chitosan derivatives for this invention are the dermatologically-compatible salts of chitosan such as those with pyrrolidone carboxylic acid, glutamic acid, acetate, etc., and also N,O-carboxymethyl chitosan.

Suitable poly(N-vinyl lactams) have a K value of at least 60, preferably at least 70, and most preferably from 80 to 110. The K value represents a function of molecular weight. The K value is derived from viscosity measurements and is calculated according to Fikentscher's formula described by Kline, G.M., "Polyvinylpyrrolidone", Modern Plastics p 157 (Nov. 1945) and is also described in General Aniline & Film Corporation Technical Bulletin 7583-033. At the same K value or molecular weight, the level of ring-opened poly(N-vinyl lactam) is an important consideration in determining whether a gel forms.

In the invention, poly N-vinyl lactams containing above certain levels of ring-opened pyrrolidone groups, when mixed with certain solutions of neutralized chitosans, form gels which may be mildly tacky. The term tacky is intended to mean having the property of being sticky to the touch or adhesive to a degree that the gel is capable of sticking to the skin while being easily removable when removal is desired.

The term poly(N-vinyl lactam) as used herein shall be understood to include homopolymers, copolymers and terpolymers of N-vinyl lactams such as N-vinylpyrrolidone, N-vinylbutyrolactam, N-vinylcaprolactam, and the like, as well as the foregoing prepared with minor amounts, for example, up to about 20 weight percent, of one or a mixture of other vinylmonomers copolymerizable with the N-vinyl lactams. Copolymers or terpolymers of poly(N-vinyl-lactam) may comprise N-vinyl-lactam monomers such as vinylpyrrolidone copolymerized with monomers containing a vinyl functional group such as acrylates, hydroxyalkylacrylates, methacrylates, acrylic acid or methacrylic acid, and acrylamides. Of the poly(N-vinyl lactam) homopolymers, the polyvinylpyrrolidone (PVP) homopolymers are preferred. Of the poly(N-vinyl lactam) copolymers, vinyl pyrrolidone, acrylamide copolymers are preferred. A suitable poly(N-vinyl lactam) terpolymer is vinylpyrrolidone, vinylcaprolactam, dimethylaminoethyl methacrylate. A variety of polyvinylpyrrolidones are commercially available. It is important, however, for the poly(N-vinyl lactam) to contain a degree of ringopened lactam groups.

A lactam may be considered to be a cyclic amide produced from an amino acid through the elimination of a molecule of water from the -COOH and -NH_2 groups. A lactam, therefore, contains a -NH-CO- group in a ring. An N-vinyl lactam has a vinyl group at the ring nitrogen and the monomer can be polymerized through the vinyl group. In a ring-opened poly(N-vinyl lactam), the vinyl backbone may be considered to remain essentially intact, but some lactam rings are opened to make available -COOH groups. The availability of these -COOH groups may be measured through base titration to determine the mole equivalents of base per mole of acid groups in a specific poly(N-vinyl lactam). Because the polymer backbone remains essentially intact, different poly(N-vinyl lactams) having the same molecular weight or K value may have different levels of ring openings. The poly(N-vinyl lactams) useful in forming the gels in the invention have a mole equivalent/mole of acid groups greater than 2.0. In the absence of opened lactam rings, the gel does not form. The poly(N-vinyl lactams) are preferably of relatively high molecular weight as indicated by a K value above about 60.

Ring opening in poly(N-vinyl lactams) may be effected by heating a solution of the poly(N-vinyl lactam) at a temperature of from 50°C to 120°C, with from 60°C to 100°C preferred, at pressure from 103.10^3 Pa (15 psi) to 1034.10^3 Pa (150 psi) for from one half hour to 10 days, with from one hour to 24 hours preferred. The solvent for the solution is preferably aqueous and may include a small amount of a weak base such as dilute ammonium hydroxide or dilute sodium hydroxide to result in a solution which is slightly basic, e.g. having a pH of 7-9, with 7-8 or 7-8.5 preferred. If time saving is an important consideration as in commercial operations, ring opening may be carried out, for example, for shorter periods of time in a reactor under conditions of high temperature and pressure, e.g. 200°C at 345.10^3 Pa (50 psi).

To form the gel, the poly(N-vinyl lactam) is mixed or blended with neutralized chitosan. At certain ratios of PVP/chitosan derivatives, a mixture of these two components forms a highly water-swellable gel within a short time of mixing.

The gel may be prepared by dissolving the poly(N-vinyl lactam) such as polyvinylpyrrolidone in aqueous solution, then adding an aqueous solution of neutralized chitosan with sufficient agitation to attain a homogenous mixture. The solvent used for the gel preparation is preferably substantially aqueous. For example, the gels may be prepared in water or in hydroalcohols such as water/isopropyl alcohol and water/ethanol. The gels form at a ratio of PVP/chitosan of from 12/1 to 2/1, preferably from 10/1 to 5/1. At higher PVP to chitosan ratios gels are formed but may lead to a sticky residue and may contain uncomplexed PVP which will leach out in water. The total polymer concentration as well as the ratios of the two polymer components at which the gel is made shows an effect on the consistency of the gel, which becomes softer at lower concentrations. Decreasing the total polymer concentration also leads to softer gels at a given PVP-chitosan ratio. The gels may be made with a total polymer content ranging from 5 to 20 wt.%, preferably from 7.5 wt.% to 15 wt.% solids. At lower solids levels or when the PVP has a K below 80, gels may form but they are not as consistent. The blend may be allowed to cure for a time of from a few seconds to 20 minutes. The time and temperature for curing are not critical. For purposes of convenience, ambient temperature may be used but the time can be shortened at elevated temperatures. The term gel is intended to mean viscous or semi-solid and jelly-like.

The preferred gels are stable and therefore maintain their physical integrity after absorbing large quantities of liquid. The gels can be sterilized by radiation sterilization. The gels are hydrophilic and capable of absorbing many times their weight in water or at least twice their weight in water. For practical application as described herein, a gel absorbs, for example, from 4 to 10 times its dry weight in water or saline solution (0.9% NaCl), depending on the ratio of PVP/chitosan. For example, at a ratio of PVP/chitosan of 2/1, the gel absorbs about 4 times its dry weight (i.e. solids weight) in saline solution; at a ratio of 10/1, it can absorb about 10 times its dry weight in saline solution.

While the exact nature of the mechanism by which the gel forms is not known, and while it is not intended to be bound by theory, it is believed to be caused by pervasive and tight hydrogen bonds between chains. The presence of the ring-opened pyrrolidones, in some undetermined way, plays an imperative role in achieving this goal.

Wetting, dispersing agents or surfactants as are known in the art, such as block copolymers of ethylene oxide and propylene oxide, may be added to the blends in an amount of from 1 to 5 weight percent, preferably from 1 to 3 weight percent, to reduce adherence to the skin.

Glycerine in an amount of from 5 to 50 weight percent, preferably from 10 to 30 weight percent may be added to the gel preparation to increase tack and pliability after drying. The glycerine is preferably mixed into the PVP solution prior to adding neutralized chitosan solution. Propylene glycol or low molecular weight polyethylene glycol may also be used.

Many different types of additional materials may be incorporated into the gels including organic salts, inorganic salts at low levels, alcohols, amines, polymer lattices, fillers, surfactants, pigments, dyes, fragrances and so forth as long as they do not interfere with gel formation. Many of these materials can be released from the gel.

The gels of this invention are especially useful as carriers for a wide variety of releasable biologicallyactive substances having curative or therapeutic value for human or non-human animals. Included among the biologically-active materials which are suitable for incorporation into the gels of the invention are hypnotics, sedatives, tranquilizers, anti-convulsants, muscle relaxants, analgesics, antipyretic agents, antiinflammatory agents, local anesthetics, antispasmodics, antiulcer agents, antivirals, antibacterials, antifungals, sympathomimetic agents, cardiovascular agents, antitumor agents, and so forth. A biologicallyactive substance is added in pharmaceutically-active amounts.

Particularly preferred as biologically-active additives are nitroglycerine, scopolamine, pilocarpine, ergotamine tartrate, phenylpropanolamine, and theophylline; also antimicrobials tetracycline, neomycin, oxytetracycline, triclosan, sodium cefazolin, silver sulfadiazine, and also salicylates such as methylsalicylate and salicylic acid, nicotinates such as methyl nicotinate, capsicum and benzocaine. When the gel is to be used, for example, for cosmetic treatment, hydrating agents such as sodium pyrrolidine carboxylic acid may be added. For a hydrating purpose, however, the large amount of water alone which can be absorbed by the hydrophilic gel serves a hydrating function to the skin.

Water-soluble and water-insoluble additives such as those described above may be initially mixed with the aqueous solvent before the gel preparation is begun, may be mixed with the aqueous solution of poly(N-vinyl lactam) or mixed with the aqueous solution of neutralized chitosan during the gel preparation. Water-soluble ingredients are preferably mixed in with the PVP prior to admixing with chitosan. Many water-insoluble ingredients can be mixed with chitosan prior to adding to PVP. One can also emulsify water insolubles by adding surfactants to either the PVP or chitosan. Alternatively, additives may be similarly mixed into the preparation after the poly(N-vinyl lactam) is blended with the chitosan. Additives may also be applied to the surface of a gel dressing, for example, by spraying, dipping, brushing or rolling.

The gel may be used to make adsorbent wound

packing agents or dressings, skin masks or wraps, drug delivery patches and dry film products.

When the gel is used as a wound packing or cavity-filling wound dressing, it advantageously provides the desired properties of such dressings, such as (1) biocompatability; (2) ability to conform to a wound cavity; (3) non-adherence to the wound: (4) absorbs exudate; (5) removable in one piece from the wound; (6) holds its physical integrity when swollen with exudate; (7) is not too sticky for handling.

When used as a skin-hydrating mask, the gel has excellent hydrating capacity, advantageously contains no alcohol, and is easily and cleanly removed.

When made into a dry film and used as a skin mask, it provides a flexible, clear, hydrophilic film which adheres to the skin when wetted with water. The film can retain active moisturizers and other ingredients close to the skin, helping in their delivery. The film can also be easily peeled off after a period of time without leaving residues.

To obtain the products invention, the gel may be packaged by itself in a mold, in a dry film form, or as a two-part system which requires mixing prior to use; or may be provided on a substrate and covered with a release liner to prevent the gel from sticking to itself. The release liner is removed prior to application to skin. The substrate may fulfill one or several functions including providing reinforcement, providing a gas and liquid barrier, providing a support with air permeability, providing protection for the gel and the area of treatment, etc. Substrate selection to provide the desired properties is known to those skilled in the art.

The gel may be coated or spread onto a backing or substrate by any means known in the art. The gel can be combined with and adhered to a virtually unlimited variety of substrates or backings including resins, metal foils, woven and non-woven webs of natural and synthetic fibers, etc. A backing which provides gas and liquid barrier properties may be a polymer film such as polyurethane. Desirable composites with the gel may also be made using films of polyester, polyvinyl alcohol, or polyvinylidene chloride. When the gel has a barrier substrate, the resulting structure has particular utility as a wound and burn dressing. Moisture is kept in and excess exudate is absorbed to promote healing but bacteria are prevented from entering the wound or burn area, and microbial stasis may be maintained through the incorporation of an anti-microbial agent into the gel to prevent infection. For ease of use, the tacky gel on a backing is covered with a release liner which may be a silicone-coated film or polyethylene.

The gel may be coated onto the backing so that the of the backing surface. If the gel occupies part of the backing surface, non-gel coated areas of the backing may be provided with an additional adhesive. A dressing of this type is positioned on the skin so that the additional skin adhesive comes into contact with intact skin while the absorbent gel contacts a wound. The additional adhesive provides a dressing with staying power when the absorbent gel has become substantially saturated with wound exudate thus losing some of its adhesiveness through a dilution effect.

In still another embodiment, the gel may be used in cosmetic preparations such as face masks and nail wraps. The gel serves a hydrating function with or without a backing and a cosmetic effect may be enhanced with the incorporation of other ingredients. A kit for a cosmetic gel may comprise a ready-made gel or two components: a poly(N-vinyl lactam) component and a chitosan component. Other cosmetic agents such as hydrating agents, fragrances, etc. can also be supplied to the ready-made gel or to either component. For use, the components may be mixed and applied. The gel advantageously can be easily peeled off after use. It shall be understood that the term cosmetic means a preparation intended to enhance or improve physical appearance.

In a further embodiment, fragrances may be incorporated into the gel. When the gel is kept moist in a suitable vented container, the fragrance is slowly released as an air freshener.

The following examples are intended to illustrate the invention.

EXAMPLE 1

A PVP with a K value of 92 was titrated with base. The results showed that the PVP had 1.4 mole equivalents/mole of acid groups. Attempts to form a gel with chitosan using this PVP were unsuccessful.

EXAMPLE 2

The PVP of Example 1 was heated in water at 60°C for eight days, then at 95°C for eight hours. This material, when titrated with base, showed 2.15 mole equivalents/mole of acid groups and formed a highly swellable gel at a weight ratio of 10 PVP/1 chitosan at 10% total polymer concentration.

EXAMPLE 3

A PVP (Luviskol-brand^{R}, BASF Corporation) having a K value of 93 was titrated with base and showed less than 1 mole equivalent/mole of acid groups. Attempts to form a gel using this PVP with chitosan were unsuccessful.

EXAMPLE 4

A commercial PVP (Kollidon 90^{R}, BASF Corporation), having a K value of 93 was titrated with base and showed 5 mole equivalents/mole of acid groups. When mixed with chitosan, this PVP forms a hydrophilic gel.

EXAMPLE 5

To 8.6 grams of a 25% water solution of PVP described in Example 4 was added 1.4 grams propylene glycol and 3.0 grams of a 20% aqueous solution of a block copolymer of ethylene oxide and propylene oxide (Pluronic F88^R, BASF Corporation). To that solution was added 5 grams of a 3% aqueous solution of chitosan neutralized with pyrrolidone carboxylic acid (Kytamer PCA, Amerchol Corporation). The mixture was stirred for one minute then applied to wet human skin. It quickly became nonflowable and could be rolled r peeled from the skin.

The gel, when put into excess water or saline solution at room temperature, absorbed additional liquid but did not dissolve or disintegrate.

EXAMPLE 6

5.0 grams of a 20% solution of PVP in water containing at least 2 mole equivalents/mole of acid containing groups were mixed with 5.0 grams of a 2% solution of N,O-carboxymethyl chitosan (NOCC^R, Nova Chem. Ltd.). The mixture was poured into a hemispherical mold. It set in 10 seconds at room temperature to a mildly tacky, non-flowable gel. The gel was pliable and relatively non-adherent to a wound.

The gel, when put into excess water or saline soluti n at room temperature, absorbed water but did not dissolve or disintegrate.

EXAMPLE 7

A solution of 5.0 g of 20% PVP containing more than 2 mole equivalents/mole of acid groups, 5 grams of deionized water, 5.0 g of 2% neutralized chitosan, 0.25 grams of polyethylene glycol (carbowax 400^R, Union Carbide Corporation) as a plasticizer and 0.25 grams of a block copolymer of ethylene glycol and propylene glycol (Pluronic F88^R, BASF Corporation) for easier release from a substrate were mixed and coated in a thickness of 1 mm on a polyester film substrate.

The coating was dried in an oven to form a 0.05 mm thick dried film that can be die cut to specific shapes, e.g., for moisturizing face masks or eye patches. Before the film is applied to skin, the skin is sprayed or wetted with water.

EXAMPLE 8

The dried film of Example 7 was soaked in water and 0.9% sodium chloride solution at room temperature. In both liquid media, the film absorbed large amounts of liquids, expanding in the process.

Claims

1. A dermatologically-compatible composition comprising a hydrophilic, semi-solid and jelly-like gel which comprises a blend of a neutralized chitosan and a hydrophilic poly(N-vinyl lactam) having a K value of at least 60 and at least 2.0 mole equivalents of available acid groups.

2. The composition of claim 1 wherein at least part of the available acid groups originate from ring-opened pyrrolidone groups.

3. The composition of claim 1 or 2, wherein the gel comprises a poly(N-vinyl lactam)/chitosan weight ratio of from 12/1 to 2/1.

4. The composition of claim 1-3, wherein the gel is prepared in an aqueous solution at a total polymer concentration of from 5 weight percent to 20 weight percent poly(N-vinyl lactam) and chitosan.

5. The composition of claim 1-4, wherein the solution comprises water or a hydroalcohol.

6. The composition of claim 1-5, which further comprises at least one substrate, preferably selected from a group consisting of polymer film, collagen film, woven fabric, and non-woven fabric.

7. The composition of claim 6, wherein the substrate is a polyurethane film, or a polyester film.

8. The composition of claim 6 or 7 wherein the substrate is stretchable.

9. The composition of claim 1-8 wherein the gel comprises at least one additional ingredient, such as a surfactant, a fragrance and/or a biologically-active material.

10. The composition of claim 9 wherein the additional ingredient is selected from a group consisting of nitroglycerine, scopolamine, pilocarpine, ergotamine tartrate, phenylpropanolamine, theophylline, tetracycline, neomycin, oxytetracycline, triclosan, sodium cefazolin, silver sulfadiazine, salicylates, nicotinates, capsaicin and benzocaine.

11. A method for preparing a stable, mildly tacky, hydrophilic, semi-solid and jelly-like gel comprising mixing an aqueous dispersed poly(N-vinyl lactam) homopolymer or copolymer having a K value of at least 60 and above 2.0 mole equivalents of available acid groups and an aqueous solution of neutralized chitosan in a poly(N-vinyl lactam)/chitosan ratio of from 12/1 to 2/1, with a total polymer content above 5 weight percent to produce a blend, allowing the blend to cure for a time of from 10 seconds to 2 hrs. until a gel is formed.

12. The method of claim 11, which further comprises treating a poly(N-vinyl lactam) to increase mole equivalents of acid groups to above 2.0 by heating the poly(N-vinyl lactam) in aqueous solution at a temperature of from 50°C to 200°C, at a pressure of from 103.10^3 Pa (15 psi) to 1034.10^3 Pa (150 psi), for one-half hour to 10 days.

13. The method of claim 11 or 12, wherein the aqueous solution has a pH of from 4 to 8.

14. The method of claims 11-13, which further comprises adding a biologically-active material to the blend.

15. The method of claims 11-14, wherein the blend is formed into a dressing by coating or casting the blend onto a substrate.

16. The method of claim 15 wherein the blend is covered with a second substrate which is a release liner.

17. The method of claims 11-16 wherein the blend is formed into a dressing by casting two separate slabs of gel onto two separate substrates, applying a solution of a biologically-active material to a surface of one of the slabs, and compressing the slabs together so that the biologically active material is located between the slabs.

18. The composition of claims 1-10 in the form of a product selected from a group consisting of wound packings, wound dressings, burn dressings, drug delivery dressings, dry films, cosmetic mask dressings and cosmetic wrap dressings.

19. The composition of claim 18 in the form of a wound packing or cavity dressing without a substrate.

20. A stable, hydrophilic, semi-solid and jelly-like gel which comprises a blend of neutralized chitosan and a hydrophilic poly(N-vinyl lactam) having a K value of at least 60 and above 2.0 mole equivalents of available groups, the chitosan and poly(N-vinyl lactam) combined in a chitosan/poly(N-vinyl lactam) weight ratio from 12/1 to 2/1 in an aqueous solution at a total polymer concentration of at least five weight percent.

Patentansprüche

1. Dermatologisch verträgliche Zusammensetzung, dadurch gekennzeichnet, daß sie ein hydrophiles, halbfestes und gallertartiges Gel umfaßt, das eine Mischung aus einem neutralisierten Chitosan und einem hydrophilen Poly(N-vinyllactam) mit einem K-Wert von mindestens 60 und mindestens 2,0 Moläquivalente verfügbarer Säuregruppen umfaßt.

2. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß mindestens ein Teil der verfügbaren Säuregruppen aus ringgeöffneten Pyrrolydongruppen stammt.

3. Zusammensetzung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß das Gel ein Poly(N-vinyllactam)/Chitosan-Gewichtsverhältnis von 12/1 bis 2/1 umfaßt.

4. Zusammensetzung nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß das Gel in einer wäßrigen Lösung bei einer Gesamtpolymerkonzentration von 5 Gew.-% bis 20 Gew.-% Poly(N-vinyllactam) und Chitosan hergestellt wird.

5. Zusammensetzung nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß die Lösung Wasser oder einen wäßrigen Alkohol umfaßt.

6. Zusammensetzung nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß sie außerdem mindestens ein Substrat, vorzugsweise ausgewählt aus der Gruppe bestehend aus einem Polymerfilm, Kollagenfilm, Gewebe und Faservließ, umfaßt.

7. Zusammensetzung nach Anspruch 6, dadurch gekennzeichnet, daß das Substrat ein Polyurethanfilm oder ein Polyesterfilm ist.

8. Zusammensetzung nach Anspruch 6 oder 7, dadurch gekennzeichnet, daß das Substrat dehnbar ist.

9. Zusammensetzung nach einem der Ansprüche 1 bis 8, dadurch gekennzeichnet, daß das Gel mindestens einen zusätzlichen Bestandteil umfaßt, wie z.B. ein oberflächenaktives Mittel, einen Duftstoff und/oder ein biologisch wirksames Material.

10. Zusammensetzung nach Anspruch 9, dadurch gekennzeichnet, daß der zusätzliche Bestandteil ausgewählt ist aus der Gruppe bestehend aus Nitroglycerin, Scopolamin, Pilocarpin, Ergotamintartrat, Phenylpropanolamin, Theophyllin, Tetracyclin, Neomycin, Oxytetracyclin, Triclosan, Natriumcefazolin, Silbersulfadiazin, Salicylaten, Nicotinaten, Capsaicin und Benzocain.

11. Verfahren zur Herstellung eines stabilen, leicht klebrigen, hydrophilen, halbfesten und gallertartigen Gels, dadurch gekennzeichnet, daß es umfaßt: Mischen eines in Wasser dispergierten Poly(N-vinyllactam)-Homopolymers oder -Copolymers mit einem K-Wert von mindestens 60 und mit mehr als 2,0 Moläquivalenten verfügbarer Säuregruppen

und einer wäßrigen Lösung eines neutralisierten Kitosans bei einem Poly(N-vinyllactam)/Chitosan-Verhältnis von 12/1 bis 2/1, bei einem Gesamtpolymergehalt von mehr als 5 Gew.-%, zur Herstellung einer Mischung und Härtenlassen der Mischung, während 10 Stunden bis 2 Stunden bis zur Ausbildung eines Gels.

12. Verfahren nach Anspruch 11, dadurch gekennzeichnet, daß außerdem das Behandeln eines Poly(N-vinyllactams) zur Erhöhung der Moläquivalente an Säuregruppen auf mehr als 2,0 durch Erhitzen des Poly(N-vinyllactams) in einer wäßrigen Lösung bei einer Temperatur von 50°C bis 200°C und bei einem Druck von $103x10^3$ Pa (15 psi) bis $1034x10^3$ Pa (150 psi) während einer halben Stunde bis zu 10 Tagen umfaßt.

13. Verfahren nach Anspruch 11 oder 12, dadurch gekennzeichnet, daß die wäßrige Lösung einen pH-Wert von 4 bis 8 besitzt.

14. Verfahren nach einem der Ansprüche 11 bis 13, dadurch gekennzeichnet, daß es außerdem das Zugeben eines biologisch wirksamen Materials zur Mischung umfaßt.

15. Verfahren nach einem der Ansprüche 11 bis 14, dadurch gekennzeichnet, daß die Mischung durch Beschichten oder Aufgießen auf ein Substrat zu einem Verbandstoff ausgebildet wird.

16. Verfahren nach Anspruch 15, dadurch gekennzeichnet, daß die Mischung mit einem zweiten Substrat, das eine abtrennbare Deckschicht ist, bedeckt wird.

17. Verfahren nach einem der Ansprüche 11 bis 16, dadurch gekennzeichnet, daß die Mischung zu einem Verbandstoff ausgebildet wird, indem man zwei getrennte Gelplatten auf zwei getrennten Substraten gießt, eine Lösung eines biologisch wirksamen Materials auf eine Oberfläche einer der Platten aufbringt, und die Platten so zusammenpreßt, daß das biologisch wirksame Material sich zwischen den Platten befindet.

18. Zusammensetzung nach einem der Ansprüche 1 bis 10 in Form eines Produktes ausgewählt aus der Gruppe bestehend aus Wundtampons, Wundverbänden, Brandwundenverbänden, wirkstoffabgebenden Verbänden, trockenen Filmen, kosmetischen Masken und kosmetischen Umhüllungen.

19. Zusammensetzung nach Anspruch 18 in Form eines Wundtampons oder Kavernenverbandes ohne Substrat.

20. Stabiles, hydrophiles, halbfestes und gallertartiges Gel, dadurch gekennzeichnet, daß es eine Mischung aus neutralisiertem Chitosan und einem hydrophilen Poly(N-vinyllactam) mit einem K-Wert von mindestens 60 und mehr als 2,0 Moläquivalenten verfügbarer Säuregruppen umfaßt, wobei Chitosan und Poly(N-vinyllactam) in einem Chitosan/Poly(N-vinyllactam)-Gewichtsverhältnis von 12/1 bis 2/1 in einer wäßrigen Lösung bei einer Gesamtpolymerkonzentration von mindestens 5 Gew.-% kombiniert sind.

Revendications

1. Composition dermocompatible comprenant un gel hydrophile, semi-solide et ayant la consistance de la gelée qui comprend un mélange d'un chitosane neutralisé et d'un poly(N-vinyl-lactame) hydrophile ayant une valeur K d'au moins 60 et au moins 2,0 équivalents en moles de groupes acide disponibles.

2. Composition selon la revendication 1, dans laquelle au moins une partie des groupes acide disponibles provient de groupes pyrrolidone décyclisés.

3. Composition selon la revendication 1 ou 2, dans laquelle le gel a un rapport en poids poly(N-vinyl-lactame)/ chitosane de 12/1 à 2/1.

4. Composition selon les revendications 1 à 3, dans laquelle le gel est préparé dans une solution aqueuse à une concentration totale de polymères de 5 à 20 % en poids de poly(N-vinyl-lactame) et de chitosane.

5. Composition selon les revendications 1 à 4, dans laquelle la solution comprend de l'eau ou un hydroalcool.

6. Composition selon les revendications 1 à 5, qui comprend en plus au moins un substrat, de préférence, choisi dans un groupe constitué d'un film de polymère, un film de collagène, une étoffe tissée, et une étoffe non tissée.

7. Composition selon la revendication 6, dans laquelle le substrat est un film en polyuréthanne, ou un film en polyester.

8. Composition selon la revendication 6 ou 7, dans laquelle le substrat est étirable.

9. Composition selon les revendications 1 à 8, dans laquelle le gel comprend au moins un ingrédient supplémentaire, tel qu'un tensioactif, un parfum et/ou une substance biologiquement active.

10. Composition selon la revendication 9, dans laquelle

l'ingrédient supplémentaire est choisi dans un groupe constitué de la nitroglycérine, la scopolamine, la pilocarpine, le tartrate d'ergotamine, la phénylpropanolamine, la théophilline, la tétracycline, la néomycine, l'oxytétracycline, le triclosane, la céfazoline de sodium, la sulfadiazine d'argent, les salicylates, les nicotinates, la capsaïcine et la benzocaïne.

11. Procédé de préparation d'un gel stable, légèrement collant, hydrophile, semi-solide et ayant la consistance de la gelée comprenant le mélange d'un homopolymère de poly(N-vinyl-lactame) dispersé aqueux ou d'un copolymère ayant une valeur K d'au moins 60 et plus de 2,0 équivalents en moles de groupe acide disponibles et d'une solution aqueuse de chitosane neutralisé, dans un rapport poly(N-vinyl-lactame)/chitosane de 12/1 à 2/1, avec une teneur totale de polymères supérieure à 5 % en poids, pour produire un mélange homogène, et le durcissement du mélange homogène pendant un laps de temps allant de 10 secondes à 2 heures, jusqu'à ce qu'un gel soit formé.

12. Procédé selon la revendication 11, qui comprend en plus le traitement d'un poly(N-vinyl-lactame) pour porter les équivalents en moles de groupes acide à plus de 2,0 en chauffant le poly(N-vinyl-lactame) dans une solution aqueuse à une température de 50 à 200°C, à une pression de 103.10^3 Pa (15 psi) à 1034.10^3 Pa (150 psi), pendant une durée allant d'une demi-heure à 10 jours.

13. Procédé selon la revendication 11 ou 12, dans lequel la solution aqueuse a un pH de 4 à 8.

14. Procédé selon les revendications 11 à 13, qui comprend en plus l'addition d'une substance biologiquement active au mélange.

15. Procédé selon les revendications 11 à 14, dans lequel le mélange homogène est formé en un pansement en enduisant ou en coulant le mélange homogène sur un substrat.

16. Procédé selon la revendication 15, dans lequel le mélange homogène est couvert avec un second substrat qui est une bande anti-adhésive.

17. Procédé selon les revendications 11 à 16, dans lequel le mélange homogène est formé en un pansement en coulant deux plaques de gel séparées sur deux substrats séparés, en appliquant une solution d'une substance biologiquement active sur une surface de l'une des plaques, et en comprimant les plaques l'une contre l'autre pour que la substance biologiquement active soit située entre les plaques.

18. Composition selon les revendications 1 à 10 sous la forme d'un produit choisi dans un groupe constitué de tamponnements pour plaies, pansements pour plaies, pansements pour brûlures, patchs de délivrance de médicaments, pellicules sèches, compresses pour masques cosmétiques et enveloppements cosmétiques.

19. Composition selon la revendication 18 sous la forme d'un tamponnement pour plaies ou d'un pansement obturateur de cavité, sans substrat.

20. Gel stable, hydrophile, semi-solide et ayant la consistance de la gelée qui comprend un mélange de chitosane neutralisé et d'un poly(N-vinyl-lactame) hydrophile ayant une valeur K d'au moins 60 et plus de 2,0 équivalents en moles de groupes disponibles, le chitosane et le poly(N-vinyl-lactame) étant combinés dans un rapport en poids chitosane/poly(N-vinyl-lactame) de 12/1 à 2/1 dans une solution aqueuse à une concentration totale de polymères d'au moins 5 % en poids.